

biotinylated polynucleotide, a polynucleotide linked to an enzyme, and a radio-labeled polynucleotide.

C7  
C8  
136. (Amended) The polynucleotide of claim 123, wherein the polynucleotide is a polynucleotide immobilized on the surface of a gene chip.

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140. (Amended) The polynucleotide of claim 123, wherein an end of the polynucleotide is nucleolytically blocked.

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**In the Drawings:**

Please substitute Figure 1A with the substitute Figure 1A provided herewith.

Please substitute Figure 2B with the substitute Figure 2B provided herewith.

Please substitute Figure 3B with the substitute Figure 3B provided herewith.

**REMARKS**

Claims 23, 24, and 100-144 are pending in the application. Claims 100-102, 112, 113, 135, and 136 have been amended to correct claim dependencies and other formal errors. No new matter is added by the amendments. The Examiner has indicated that claims 23 and 24 are allowable.

An amended substitute Sequence Listing, correcting the formal errors as described in the Notice to Comply and in Paper No. 19 is also submitted. The amendments to the Sequence Listing are not new matter. Support for the SEQ IDS NOs: 65-71 is found at least in Figure 3B as originally filed.

Figures 2B, and 3B have been amended to insert corrections of a clerical nature; such amendments do not constitute new matter. Support for the amendments to the drawings is found at least in Figures 2B and 3B, as filed, and in the specification at page 15, line 4, and page 96, line 7.

Marked up versions of the amended specification, Sequence Listing, drawings and claims, showing the changes made, are submitted herewith pursuant to 37 C.F.R. § 1.121.

Each of the points raised in Paper No. 19 is addressed below in the order it was presented in the Office Action.

***I. Priority.***

At page 2-3 of Paper No. 19, the Examiner has asserted that the specification of U.S. provisional application no. 60/121,537 is not enabling for invention as claimed. The applicants disagree with this assertion, for at least the reasons set forth below.

None of the art presently cited against the application has a prior art date before February 25, 2000; thus, at this point in the prosecution of the application; however, the applicants submit that the disclosure of the '537 application fully enables all of the claims in the present application under 35 U.S.C. § 112 for at least the following reason. The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent, coupled with information known in the art, without undue experimentation. M.P.E.P. 2164.01, *citing United States v. Teletronics, Inc.*, 857 F.2d 778, 785 (Fed. Cir. 1988). In the disclosure of the '537 application is provided an entire nucleotide sequence of SEQ ID NO: 1. *See, e.g.*, Figure 5A. The disclosure, therefore, contains all isolated polynucleotides within the scope of the claims. The skilled artisan is enabled to make all of the presently claimed *FEZ1* polynucleotides, as well as many others that are not claimed. Based upon the disclosure of the '537 patent and routine techniques as known in the art at the time of filing of the '537 application, a person of skill could have easily prepared the claimed polynucleotides, animal cells, kits and pharmaceutical compositions.

Accordingly, for at least the reasons above, all pending claims in the present application are properly accorded the effective filing date of February 25, 1999, pursuant to § 119(e). Accordingly, the applicants respectfully request that the Examiner reconsider and withdraw the assertion that the present claims are only entitled to an effective filing date of February 25, 2000.

***II. Sequence Compliance - Notice to Comply.***

At pages 3-4 of the Office Action, the Examiner has stated that the computer readable format of the sequence listing submitted with the application containing errors. Namely, numeric identifier <160> is incorrect and, with respect to SEQ ID NO: 64, the Examiner

has stated that numeric identifier <223> is not a correct description of the artificial sequence. Further, the Examiner has pointed out that the sequences in Figure 3B are not assigned sequence identification numbers, either in the figure itself or in the Brief Description of the Drawings.

A substitute sequence listing is submitted, containing a correction to numeric identifier line <160> and including the cDNA sequences shown in Figure 3B, designated SEQ ID NOs: 65-70. The specification has also been amended accordingly.

No new matter is added by this addition to the Sequence Listing, as support for the new sequences SEQ ID NOs: 65-70 is found at least in Figure 3B as originally filed. It is respectfully requested that the Examiner reconsider and withdraw his statement that the sequence listing is non-compliant.

The applicants disagree with the Examiner's assertion that Description of the artificial sequence at the numeric identifier <223> with respect to SEQ ID NO: 64 is non-compliant. The sequences identified at SEQ ID NOs: 61 to 64 are theoretical, exemplary sequences provided in the specification of the application to illustrate the applicants' intended definition of the term "adjacent" when referring to two or more polynucleotide portions. *See*, specification at page 26, lines 7-12. The applicants are entitled to describe the disclosed sequences in any manner they desire, so long as such description is accurate. In the present case, the sequence SEQ ID NO: 64 is an example sequence. It is theoretical, there is no "source."

For the reasons given above, it is respectfully requested that the Examiner reconsider and withdraw the objections.

A copy of a Declaration under § 1.181 *et seq.* and a copy of the Notice to Comply are submitted herewith. Also enclosed is a marked-up version of the specification showing the changes made.

### ***III. Objections to the Drawings.***

At page 4, the Examiner has indicated that the corrected drawings, received on December 17, 2001, are "not acceptable." The Examiner asserts that "Figure 5 has panels A-Q, while in the as-filed specification, . . . Figure 5 is described as having panels A-P." Therefore, the Examiner reasons that a "new" panel has been added. The applicants disagree with the Examiner's assertion of unacceptability.

Panel Q of Figure 5 is not new matter. First, the inclusion of any of the panels of Figure 5 does not constitute matter as a substantially identical Figure 5, including all of the panels now designated A-Q, is present in the U.S. provisional application to which this application claims priority, U.S. Application Serial No. 60/121,537, filed February 25, 1999. Further, the '537 application is expressly incorporated into the instant application by reference. *See*, page 124, lines 3-4, of the specification. Additionally, all of the information provided in Figure 5Q (a DNA sequence) was provided with the application as initially filed in the Sequence Listing (SEQ ID NO: 21). *See, also*, the specification at page 18, lines 23-25 ("Figure 5Q lists the nucleotide sequence (SEQ ID NO: 21) of the F37 probe described herein.")

The panel Q to which the Examiner refers is clearly described in the specification of the present application at page 18, lines 23-25 (see above). That page 17, line 21 of the as-filed application contains a typographical error which describes Figure 5 as "comprising Figure 5A-5P" is not relevant to new matter analysis under § 132. The applicants note that this typographical error has been corrected in the previous amendment, filed December 17, 2001. Accordingly, the applicants respectfully submit that the drawings that are Figure 5, panels A-Q, are fully compliant and request that they be accepted.

The Examiner has enclosed a PTO Form 948 - Notice of Draftspersons Patent Drawing Review, in which Figure 1A is objected to by the draftsman as it is not properly labeled. Specifically, the draftsman asserts that the individual panels of Figure 1A should be labeled as Fig. 1A-1-1A-8. The applicants have amended the drawings and the specification to reflect this change. No new matter is added by the amendment.

Accordingly, the applicants respectfully submit that the drawings are now fully compliant with 37 C.F.R. § 1.84(h). In view of the above, it is requested that the Examiner reconsider and withdraw the objections to the drawings.

#### ***IV. Specification.***

##### ***A. New Matter Under 35 U.S.C. § 132.***

At pages 4-5 of Paper No. 19, the Examiner objects to the amendment filed December 17, 2001 under 35 U.S.C. § 132, asserting that it introduces new matter into the disclosure. Specifically, the Examiner specifies that the added material which is not supported by the original disclosure is a "new" panel Q that has been added in the Brief Description of the

Drawings for Figure 5, whereas, according to the Examiner, in the as-filed specification only panels A-P were described. Second, the Examiner appears to be asserting that the entire Figure 5, provided in the previous response, constitutes new matter. The Examiner requests cancellation of the alleged new matter. The applicants traverse this objection, and decline to cancel the subject matter.

First, the amendment to the Brief Description of the Drawings allegedly adding a new panel Q does not constitute new matter. As described above, panel Q is clearly described in the specification of the present application at page 18, lines 23-25 and SEQ ID NO: 21, as filed. Thus, the correction of the typographical error at page 17, line 21, does not constitute new matter.

Additionally, the submission of Figure 5 does not constitute the addition of new matter to the present application. All panels of Figure 5 are merely nucleic acid sequences. Each of these sequences was present in the initial application, as filed, at least in the original Sequence Listing (designated SEQ ID NOs: 1, 2, 9-14, 3, 4, 15-20, and 21), and in the specification at page 17, line 21 to page 18, line 24.

Furthermore, a substantially identical Figure 5 is present in the '437 application. The '437 application is incorporated by reference into the present disclosure. *See*, the specification at page 124, lines 3-4.

Accordingly, neither the amendment to the Brief Description of the Drawings nor Figure 5 constitutes new matter to the application. It is requested that the examiner reconsider and withdraw the objection under 35 U.S.C. § 132.

***B. Objection related to "KIA0522" label in Figure 2B.***

At page 5 of the Office Action, the Examiner has clarified the objection relating to the inconsistency between the protein called "KIAA0522" in the specification at, *e.g.*, page 15, line 4, and that which is labeled in Figure 2B.

The applicants have submitted a corrected version of Figure 2B, wherein the protein is properly labeled as "KIAA0522". This amendment of the drawing does not constitute new matter, as it is merely a typographical correction, and the protein having the proper sequence correlated with the proper label is present in the disclosure at least in SEQ ID NO: 8 and at page 15, line 4, and page 96, line 17.

Accordingly, it is respectfully requested that the Examiner reconsider and withdraw the objection.

***V. Objections to Claims 102 and 140.***

At page 6, the Examiner has objected to claim 140 because a space is missing in the phrase “claim123”. The applicants have amended claim 140 to correct this informality.

The Examiner has objected to claim 102 as being of improper dependent form, asserting that it fails to further limit the subject matter of the previous claim. While the applicants do not necessarily agree with the Examiner, they have amended claim 102 to further clarify the claimed subject matter, in order to facilitate the prosecution of this application.

Claim 102 is a proper dependent claim. As a dependent claim, claim 102 incorporates the elements of claim 100. Claim 102 is directed to an isolated polynucleotide having a sequence. The sequence of the claim 102 polynucleotide comprises at least 100 consecutive nucleotide residues of SEQ ID NO: 1, and includes a portion of a strand of SEQ ID NO: 1. The “portion,” in turn, includes a residue selected from any of the specified residues of SEQ ID NO: 1. Therefore, it is submitted that claim 102, as amended, is a proper dependent claim, is further limiting of claim 100, and does not include embodiments that are not encompassed by the claim 100. Claim 101 has been similarly amended for purposes of consistency.

Accordingly, it is respectfully requested that the Examiner reconsider and withdraw the objections relating to claim 140 and claim 102.

***VI. Rejections Under 35 U.S.C. § 112, first paragraph: Enablement.***

At page 7-12, the Examiner has rejected claims 118-121, 141, 142, and 144 under 35 U.S.C. § 112, first paragraph. As basis for the rejection, the Examiner asserts that the claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains or with which it is connected to make and/or use the invention. The Examiner, in formulating the rejection, performs a *Wands* analysis, with particular focus on the alleged “complete lack of documented success for any gene therapy.” The applicants respectfully traverse the rejection.

As a threshold matter, the applicants point out that the Examiner has expressly indicated that this rejection is on the grounds of enablement. However, the applicants note that the Examiner's analysis focuses primarily on what the Examiner perceives is an underlying lack of operability or utility, because of the alleged lack of success of gene therapy. The Examiner's analysis does not address any alleged absence of information in the specification which would allow a person of ordinary skill to make and use the invention, the correct test of enablement, but merely couches the operability rejection in a *Wands* analysis.

The applicants respectfully point out that, should the Examiner chose to maintain this rejection based on the reason present in Paper No. 19, it is improper to impose a 35 U.S.C. § 112, first paragraph, rejection grounded in "lack of utility" unless an appropriate basis exists for imposition of the rejection under 35 U.S.C. § 101, which does not exist in the present situation. M.P.E.P. 2107.01. To lack utility under § 101, the claimed invention must be totally incapable of achieving a useful result. M.P.E.P. § 2107, citing *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571. The journal articles cited by the Examiner in fact prove the Examiner's assertion to be incorrect; each shows that, in certain situations, "gene therapy" is inefficient. However, none shows that it is totally incapable of achieving a useful result. Further, the applicants are required to demonstrate only one utility; the fact that an animal cell maybe used in a method for "gene therapy" does not, even under the Examiner's analysis, make it non-enabled subject matter, as additional uses for transected animal cells are known and discussed in the specification.

Further, under the correct enablement analysis, as set forth by the Court of Appeals for the Federal Circuit and the M.P.E.P., the specification of the invention as claimed, is fully enabling of the claims. Enablement, under § 112, requires only that one reasonably skilled in the art could make or use the invention, based upon the disclosures in the patent coupled with information known in the art, without undue experimentation. M.P.E.P. 2164.

A person of ordinary skill, based upon the disclosure provided therein and given the sequences of peptides and/or nucleic acid molecules provided in the application, would find it well within the purview of routine skill to prepare pharmaceutical compositions and/or transfect animal cells, in order to arrive at the claimed invention. See, *e.g.*, the specification at pages 36-37 and 60-79. The specification provides the primary sequences for a the claimed polynucleotides, as well as examples for the preparation and screening of such molecules and the

peptides that can be expressed from these same polynucleotides. *Id.* Techniques for the preparation, identification and insertion of such molecules into eukaryotic cells was well known in the art at the time the application was filed.

The Examiner has apparently concluded that claims 118-121, 141, 142, and 144 are non-enabled by considering four of the eight *Wands* factors. No analysis is provided as to whether the person of skill could make and use the invention based upon the disclosure and the information available in the art. A consideration of the *Wands* factors may be useful in an enablement determination, but is by no means the sole analysis by which issues of undue experimentation can be evaluated. M.P.E.P. 2164.01(a). Further, *Wands* does not provide an analytical framework for determinations of enablement, but only for analysis of whether, the experimentation, if any, required to practice an invention, is undue. Additionally, in forming the conclusion that experimentation required is undue, one must weigh all of the *Wands* consideration. M.P.E.P. 2164.01(a), *citing In re Wright*, 999 F.2d 1557, 1562 (Fed. Cir. 1993).

The Examiner has not met her burden of showing that any experimentation is undue, as the analysis fails to consider the evidence of enablement as a whole, as required under the law, but is rather based upon an apparent prejudice against so-called “gene therapy” inventions. Further, the Examiner’s analysis regarding the four *Wands* factors she does discuss is incorrect and relies upon inapplicable technological generalizations, for which she provides neither technical nor legal support. For example, the Examiner states that the invention of claims 118-121, 141, 142, and 144 are drawn to a “therapeutic use [that] is a method of gene therapy,” and proceeds to present arguments that “gene therapy” is ineffective. Based on the references cited by the Examiner, the applicants can assume that by “gene therapy” the Examiner means insertion of the claimed polynucleotide into a host genome and subsequent expression of such polynucleotide.

The Examiner concedes that the relative skill in the art is high. This high level of skill favors the applicant, as a greater quantity/complexity of experimentation is considered routine in high skill disciplines. The Examiner states that the “art of the invention” is unpredictable. This is an incorrect application of *Wands*; the inquiry is not whether the general area of technology is “predictable”, but whether the techniques and information known and available in the art provide a reliable and reproducible basis for the practice of the invention, when coupled with the disclosure of the specification. M.P.E.P. 2164.04. In the present case, the



technology related to the production of polynucleotides, pharmaceutical manufacture and the preparation of eukaryotic cells containing exogenous DNA was predictable.

Thus, the Examiner's *Wands* analysis provided no basis for a finding of non-enablement. Further, for at least the reasons given above, the specification is fully enabling for all pending claims. It is requested that the Examiner reconsider and withdraw the § 112, second paragraph, rejection for lack of enablement.

***VII. Rejections Under 35 U.S.C. § 112, first paragraph: New Matter.***

At page 12-13, the Examiner has made a "new matter" rejection under 35 U.S.C. § 112, first paragraph, asserting that claims 100-143 are not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors at the time the application was filed had possession of the claimed invention. Specifically, the Examiner asserts that the specification does not teach the "subsets" recited in claims 100 and 123. Accordingly, reasons the Examiner, these "subsets" are new matter, and must be removed from the claims. The applicant respectfully traverses the rejection.

The original application, as filed, contained a full sequence of the human *FEZ1* gene (SEQ ID NO: 1). Each of the claimed polynucleotides (which are portions of or homologous to sequences of SEQ ID NO: 1, containing the recited residue(s)) were disclosed at least as part of SEQ ID NO: 1. The initially disclosed sequence included all of the 'sub'; sequences identified in the priority applications. This subject matter included both the "subsets" for polynucleotides that are presently claimed and those that are not present claimed. Thus, the applicants have disclosed a broad range of polynucleotides – the polynucleotides claimed are not new matter. The applicants can identify no clearer way to indicate "possession" of the invention that to provide the primary nucleic acid sequence. The written description requirement under § 112 is satisfied when a primary sequences of the claimed polynucleotide is provided.

For at least the reasons above, it is requested that the Examiner reconsider and withdraw the rejection.

***VIII. Rejection Under 35 U.S.C. § 112, second paragraph.***

At pages 13-15, the Examiner has rejected claims 100-122, 126-132, 135, and 136 under 35 U.S.C. § 112, second paragraph. As basis for the rejection, the Examiner asserts that

the claims are indefinite for failing to point out and distinctly claim the subject matter which the applicant regards as the invention.

The Examiner states that it is unclear how a nucleic acid molecule can comprise at least 20 consecutive nucleic acid residues of a portion of a strand of SEQ ID NO: 1 selected from certain residues. The applicants traverse this rejection; claim 100 is not “unclear.”

The claims are directed to a polynucleotide having a sequence. The sequence has at least twenty consecutive nucleotide residues of a portion of SEQ ID NO:1. The portion of SEQ ID NO: 1 includes a residue selected from the residues specified in the so-called “subsets.” The claim does not lack clarity.

With respect to claim 100, the Examiner asserts that claim 100 is vague and indefinite in reciting residues 6939 and 7633. The amendment has been corrected to substitute “to” instead of “and”, and the applicants thank the Examiner for pointing out the typographical error.

Additionally, the Examiner asserts that claims 112, 113, 135, and 136 are vague and indefinite in reciting “an immobilized polynucleotide” as a member of the Markush group of detectably labeled isolated polynucleotides. While not necessarily agreeing with the Examiner, in order to facilitate the prosecution of this application, applicants have deleted “an immobilized polynucleotide” from the Markush group.

The Examiner has rejected claims 126 and 127, asserting it is unclear how a twenty residue isolated polynucleotide can comprise a sequence of SEQ ID NOs: 1 or 3 which are greater than twenty nucleotide residues. The applicants respectfully traverse this rejection.

Claims 126 and 127 depend from claim 123, and as such, incorporate each element of claim 123. Claim 123 does not claim a twenty residue nucleic acid molecules, rather it claims an isolated polynucleotide having a sequence that is substantially homologous to twenty consecutive nucleotide residues of a portion of at least one strand of SEQ ID NO: 1. The portion contains at least one of the nucleic acid residues recited in the claim.

Accordingly, for at least the reasons given above, it is respectfully requested that the Examiner reconsider and withdraw the rejection.

#### ***IX. Rejection Under 35 U.S.C. § 102(e) Based Upon Chader.***

At pages 15-16, the Examiner has rejected claims 100, 110-112, 113, 123, and 133-135 under 35 U.S.C. § 102(e), asserting that the claims are anticipated by U.S. Patent No. 5,840,686 of Chader ("Chader"). The Examiner asserts that Chader teaches an isolated nucleic acid sequence comprising a sequence "identical to residues 7126-7147 of SEQ ID NO: 1." The applicants respectfully traverse this rejection.

Chader does not teach each element of the invention, as presently claimed, and therefore does not anticipate it. Chader teaches only a sequence of nucleotide residues that are those of residues 7126 to 7147 of SEQ ID NO: 1. Chader does not teach each element of the isolated polynucleotide as claimed; namely, Chader does not teach an isolated polynucleotide having a sequence that comprises at least 20 consecutive nucleotide residues of a portion of a strand of SEQ ID NO: 1, wherein the portion includes a residue selected from the group consisting of the recited residues. Additionally, Chader does not teach an isolated polynucleotide that is substantially homologous to at least 20 nucleotide residues of the portions of SEQ ID NO: 1 as recited in the claim; (iii) a pharmaceutical composition comprising one of these isolated polynucleotides; (iv) an animal cell containing one of these isolated polynucleotides; and (v) several kits containing the isolated polynucleotides. Chader does not disclose the isolated polynucleotides, the kits, or the animal cells of the invention. Therefore, it does not anticipate the invention.

In view of the foregoing, it is respectfully requested that the Examiner reconsider and withdraw the § 102 rejection based upon Chader.

***X. Rejection Under 35 U.S.C. § 102(e) Based Upon Ishii.***

At page 16, the Examiner has rejected claims 100-104, 110-112, 114, 122-127, 132-135, 137, and 143 under 35 U.S.C. § 102(e) as being anticipated by Ishii. As discussed in the previous Office Action, Ishii is not prior art to this application under any subpart of 35 U.S.C. § 102(e). Ishii describes the inventors' own work. Each of the claims was invented by one or both of Carlo M. Croce and Hadeshi Ishii, the named inventors of the inventions described in this application and the authors of Ishii. The remaining authors of the Ishii reference were merely coauthors and did not invent the subject matter of the pending claims.

An executed declaration establishing those facts was submitted to the U.S. Patent and Trademark Office via facsimile on November 21, 2001, after a telephone interview with the

Examiner. A copy of the same, including the transmittal sheet and the fax confirmation, is enclosed herewith. Accordingly, it is respectfully requested that the Examiner reconsider and withdraw the rejection based upon Ishii.

### CONCLUSION

It is respectfully submitted that the drawings and sequence listing are fully compliant with the relevant rules. Additionally, the pending claims are patentably distinguished over the cited prior art, and are fully compliant with § 112. The Examiner has already indicated that claims 23 and 24 are allowable. Reconsideration and allowance of claims 100-144 are respectfully requested.

Respectfully submitted,

**CARLO M. CROCE ET AL.**

11 September 2002 By: Kristyne A. Bullock  
(Date) **KRISTYNE A. BULLOCK**  
Registration No. 42,371  
**AKIN, GUMP, STRAUSS, HAUER & FELD, L.L.P.**  
One Commerce Square  
2005 Market Street - Suite 2200  
Philadelphia, PA 19103  
Telephone: (215) 965-1200  
**Direct Dial: (215) 965-1348**  
Facsimile: (215) 965-1210

GDC:KAB: vj

Enclosures: *Petition for Extension of Time*  
*Notice of Appeal*  
*Marked-Up Version of Amended Specification Paragraph*  
*Marked Up Version of Fig. 1A*  
*Marked-Up Version of Fig. 2B*  
*Marked-Up Version of Fig. 3B*  
*Substitute Fig. 1A ("clean")*  
*Substitute Fig. 2B ("clean")*  
*Substitute Fig. 3B ("clean")*  
*Copy of Notice to Comply*  
*Substitute Sequence Listing (Paper)*  
*Substitute Sequence Listing (Computer-readable)*  
*Marked Up Version of Sequence Listing Showing the Changes Made*  
*Declaration under 37 C.F.R. 1.181 et seq.*

*Copy of Previously Submitted Declaration of Carlo M. Croce and associated papers*

**Marked-Up Version of Specification and Claims**

**U.S. Patent Application No. 09/513,888**

Shown below is a marked up version of the amended specification and claims, illustrating the changes made. Please note that deletions are indicated by brackets and insertions are indicated by underlining.

Paragraph beginning at page 13, line 25, to page 14, line 5.

Figure 1A, comprising ~~Figures 1Ai-1Aviii~~Figures 1A-1 to 1A-8, is a series of representative LOH analysis results obtained using tissue samples obtained from two patients, designated E26 and E46. ~~Figures 1Ai, 1Aiii, 1Av, and 1Avii~~Figures 1A-1, 1A-3, 1A-5, and 1A-7 depict results from tissue obtained from patient E26. ~~Figures 1Aii, 1Aiv, 1Avi, and 1Aviii~~Figures 1A-2, 1A-4, 1A-6, and 1A-8 depict results from tissue obtained from patient E46. In each figure, fluorescent PCR products were generated by amplification of DNA obtained from normal (N) and tumor (T) tissue samples from the corresponding patient, and products were separated by size. For each tracing, the horizontal axis represents DNA fragment size, and the vertical axis (i.e. peak height) represents relative amount of each fragment. Several fragment sizes (in base pairs) are indicated.

Paragraph beginning at page 16, line 11 and ending at page 16, ~~line 25~~.

-- Figure 3B, comprising ~~Figures 3Bi-3Bvi~~Figures 3B-1 to 3B-4, is a series of sequence chromatograms of *FEZ1* genes obtained from three individuals having mutated *FEZ1* genes, represented by SEQ ID NOs: 65 to 71. As indicated in ~~Figure 3Bii~~ (SEQ ID NO: 66), a point mutation in *FEZ1* (TCC/Ser → CCC/Pro) at codon 29 was identified in ~~an~~ a primary esophageal cancer tissue sample obtained from patient E44. Nucleotide sequences from normal

DNA from patient E44 (N) and from a BAC contig (B) are shown for comparison. A bold line overlies the altered codon. In a primary esophageal cancer tissue sample obtained from patient E50, a point mutation in *FEZ1* (AAG/Lys → GAG/Glu) was detected at codon 119 was found, as indicated in ~~Figure 3B-iv~~ Figure 3B-4 The normal BAC sequence chromatogram is shown in Figure B-3 ~~Figure 3B-iii~~ (SEQ ID NO: 67). A third point mutation in *FEZ1* (CAG/Gln → TAG/STOP) at codon 501 was identified in prostate cancer cell line PC3, as indicated in ~~Figure 3B-vi~~ Figure 3B-6 (SEQ ID NO: 70), in which the sequence chromatogram 3'- to 5'- direction. Repeated sequencing indicated the presence of a weak signal corresponding to guanine (G) within a large adenine (A) signal in the first nucleotide at codon 501, suggesting that a fraction of the cancer cells retained the normal *FEZ1* allele. Figure 3B-1, 3B-4, and 3B-5 represent SEQ ID NOs: 65, 68, and 69, respectively. --

**In the Claims:**

100. (Amended) An isolated polynucleotide having a sequence comprising at least twenty consecutive nucleotide residues of a portion of a strand of SEQ ID NO: 1, wherein the portion includes a residue selected from the group consisting of residues 1 to 423, residues 871 to 4343, residues 4365 to 4419, residues 4451 to 4473, residues 4514 to 6917, ~~residues 6939 and to 7633~~ residues 6939 to 7125, residues 7148 to 7633, and residues 7806 to 8520 of SEQ ID NO: 1.

101. (Amended) The polynucleotide of claim 100, wherein the sequence comprises at least fifty consecutive residues of the portion of the strand of SEQ ID NO: 1.

102. (Amended) The polynucleotide of claim 100, wherein the sequence comprises at least one hundred consecutive residues of the portion of the strand of SEQ ID NO: 1.

112. (Amended) The polynucleotide of claim 111, wherein the detectably-labeled polynucleotide is selected from the group consisting of ~~an immobilized polynucleotide~~, a polynucleotide linked to a protein of a protein-ligand pair, a polynucleotide linked to a ligand of a protein-ligand pair, a biotinylated polynucleotide, a polynucleotide linked to an enzyme, and a radio-labeled polynucleotide.

113. (Amended) The polynucleotide of claim 112, wherein the ~~detectably-labeled~~ polynucleotide is ~~an immobilized~~ polynucleotide immobilized on the surface of a gene chip.

123. (Amended) An isolated polynucleotide comprising a sequence that is substantially homologous with twenty consecutive nucleotide residues of a portion of at least one strand of SEQ ID NO: 1, wherein the portion is selected from the group consisting of residues 1 to 423, residues 871 to 4343, residues 4365 to 4419, residues 4451 to 4473, residues 4514 to



6917, ~~residues 6939 and 7633~~, residues 6939 to 7125, residues 7148 to 7633 and residues 7806 to 8520 of SEQ ID NO: 1.

135. (Amended) The polynucleotide of claim 134, wherein the detectably-labeled polynucleotide is selected from the group consisting of ~~an immobilized polynucleotide~~, a polynucleotide linked to a protein of a protein-ligand pair, a polynucleotide linked to a ligand of a protein-ligand pair, a biotinylated polynucleotide, a polynucleotide linked to an enzyme, and a radio-labeled polynucleotide.

136. (Amended) The polynucleotide of ~~claim 135~~claim 123, wherein the ~~detectably-labeled~~ polynucleotide is ~~an immobilized~~ polynucleotide immobilized on the surface of a gene chip.

140. (Amended) The polynucleotide of ~~claim 123~~, claim 123, wherein an end of the polynucleotide is nucleolytically blocked.